Risk-based Monitoring in Clinical Trials

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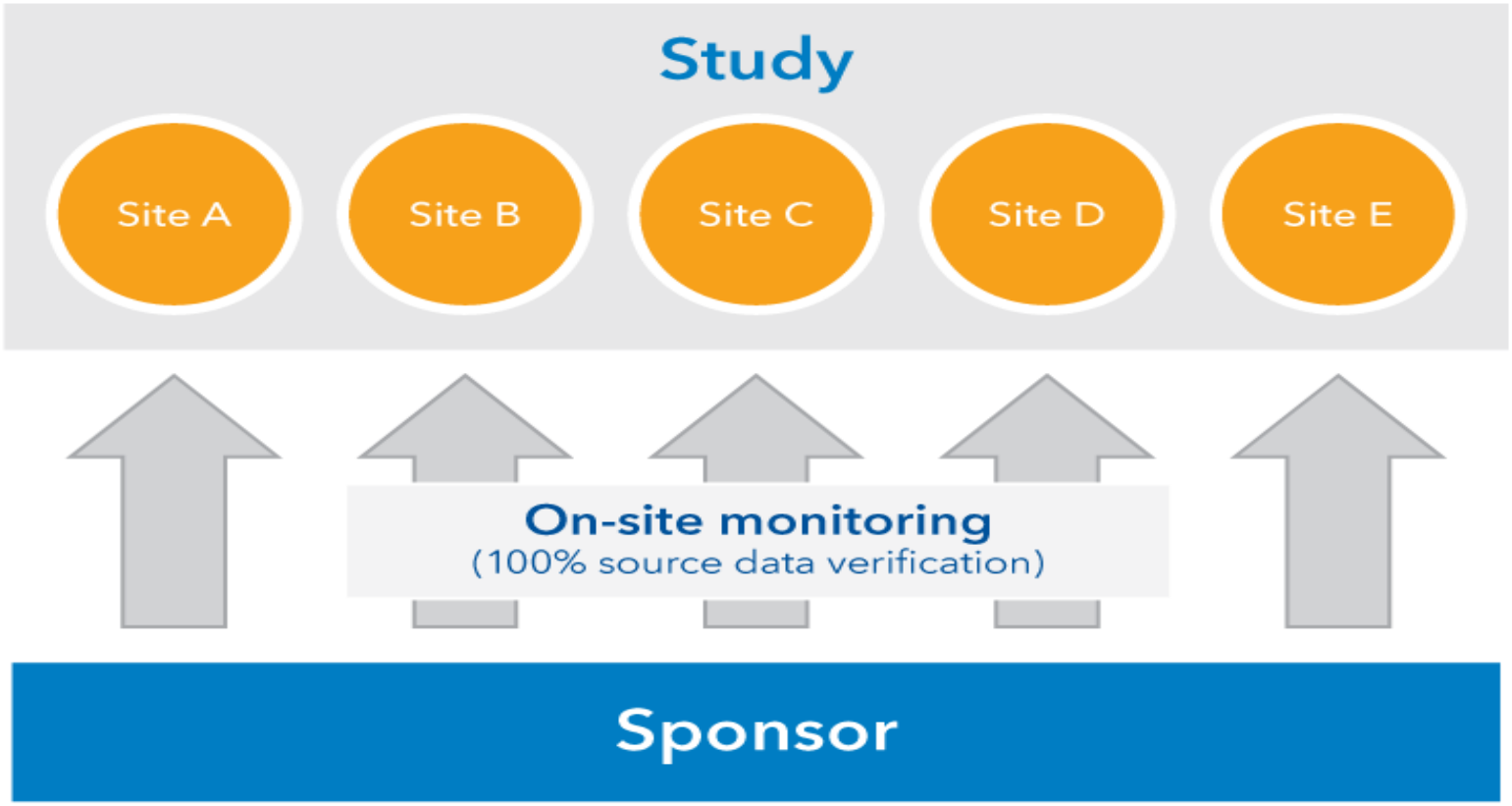
What is Risk-based Monitoring?

- **Process** of ensuring the quality of clinical trials
  - by identifying, assessing, monitoring and mitigating the risks that could affect the quality or safety of a study

- **An adaptive approach** to clinical trial monitoring that directs monitoring focus and activities to the evolving areas of greatest need which have the most potential to impact subject safety and data quality



Traditional Monitoring Process

Relies on 100% source data verification (SDV) & on-site monitoring

Source Document Verification (SDV)

- Process by which data within the case report form (CRF) or other data collection systems are compared to the original source of information (and vice versa) to confirm that the data were transcribed accurately

On-site Monitoring

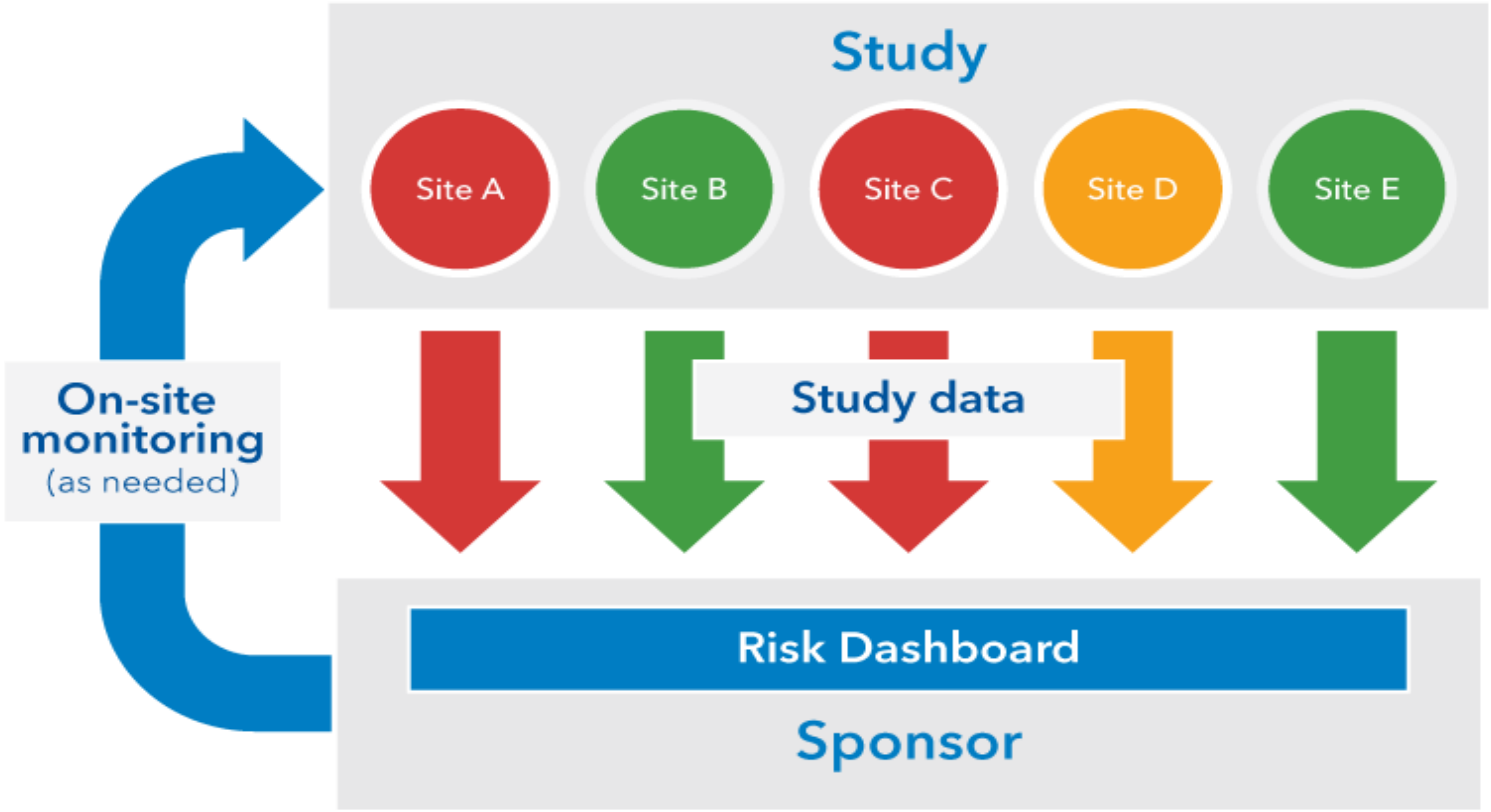
- An in-person evaluation carried out by sponsor personnel or representative(s) at the site(s) at which the clinical investigation is being conducted

Source Data Review (SDR)

- Review of source documentation to check quality of source, review protocol compliance, ensure the Critical Processes and source documentation to ascertain Investigator involvement and appropriate delegation, and assess compliance to other areas (e.g. SOPs, ICH GCPs)

Pitfalls of traditional monitoring

- Lack of real-time reporting & timeliness of data entry, leading to delay in the review of site data
- 100% SDV is not effective at identifying material risk.
- It's applied uniformly throughout a trial rather than proportionate to risks.
- Resource-intensive
- Limited in an ability to identify issues quickly & prevent them from recurring
- RMB was driven by the current ICH E6(R2) Guideline for Good Clinical Practice in November, 2016.



Risk-based Monitoring

- Employ Centralized and Off-site mechanisms
- Monitor important study parameters holistically
-Use adaptive On-site Monitoring to further support site processes, subject safety, & data quality

Central Monitoring

- A remote evaluation carried out by sponsor personnel or representatives (e.g. Data Manager, Statistician, or Monitor).

Off-site Monitoring (Remote Monitoring)

- Includes monitoring activities either within process documents or in the Monitoring Plan that occur away from the study site location (e.g. at a Monitor's home or in a sponsor representative's office).

Risk dashboard (Center of RBM)

- To provide, at a glance, information about the status of each study site relative to the specific risk factors in the trial
- designed to provide obvious visual signals for high-risk trial sites

Three different types of monitoring

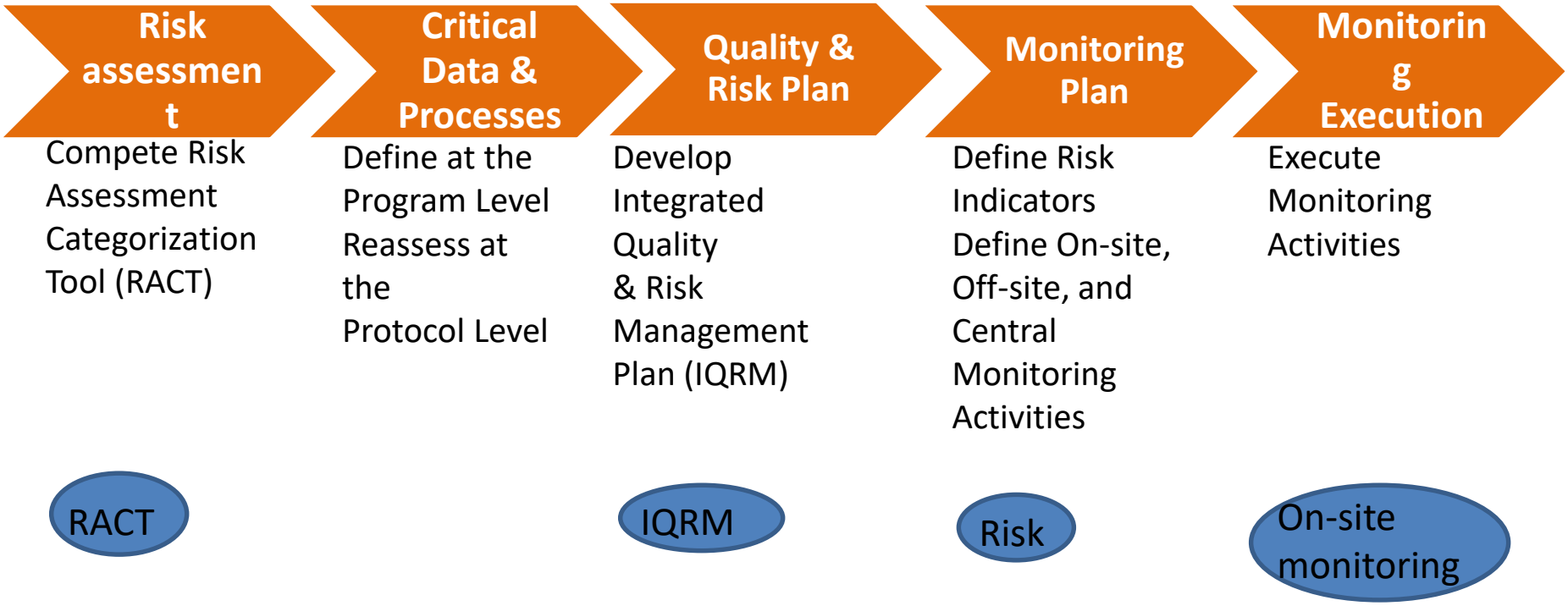
Central Monitoring	Off-site Monitoring	On-site Monitoring
Ongoing review of report & data related to key risks	Additional review of data related to risks triggered or issues identified during central monitoring	On-site monitoring for planned SDV & SDR and other on-site monitoring activities
	Site contact to get additional data related to risks triggered or issues	Further monitoring/ assessment of risk alerts/issue identified during central monitoring
	Remote site contact to control/mitigate risks triggered or issues	Control/mitigate risks triggered or issues identified

Benefits of using centralized monitoring techniques

- **Fewer errors**
  - uses more automated reviews to determine the need for manual intervention and is more likely to uncover errors
- **Lower cost**
  - can be limited to study sites where problems are most likely occurring, which can dramatically reduce the cost of monitoring
- **Better analysis**
  - With all data flowing into a central risk dashboard, statistical and graphical checks can much more easily be used to determine the presence of outliers or unusual patterns in the data
- **Cross-site comparison**
  - Compare data between sites to assess performance, identify potentially fraudulent data, or mis-calibrated equipment
- **More timely results**
  - Possible to identify and resolve issues while the trial is ongoing

Risk-based Monitoring Methodology

Methodology for Risk-Based Monitoring



TransCelerate Biopharma Inc. Risk-Based Monitoring Methodology Position Paper – RACT Tool, 2014.

1. Risk Assessment

- Vary study to study and depend on complexity of the study, type of sites, experience of sites, type of patient population, geographies involved, and safety aspects of study drug/device etc.

- These risks would be related to processes, people, systems, and technology involved in the study.

- Based on the assessment, these risks would be categorized as high/critical, medium or low risks.

- This categorization of risks (overall risk levels) will influence some of the monitoring aspects, especially extent of onsite monitoring and guide the application of a baseline monitoring approach.

2. Critical Data and Processes

- Data that support primary and key secondary objectives
- Data critical to subject safety (e.g. serious adverse events, other events leading to discontinuation of treatment)
- Processes that support subject safety and ethical treatment (e.g. seeking appropriate medical consultation or scheduling extra visits/procedures in the event of significant clinical or laboratory findings)
- Processes that support data quality (e.g. blinding, referring events for resolution, controlling inter-observer variation)
- When defining Critical Data, Cross-functional collaboration is necessary.

3. Risk Indicators

- Risk Indicators (Critical Data and other study variables to be assessed) should be assigned with Thresholds (the level, point, or value) which once reached, are designed to trigger an action such as increased data scrutiny or site follow-up (e.g. telephone call or visit to the site).

- Risk Indicators and associated Thresholds and actions are also documented in the IQRMP.

- As with all other components of the IQRMP, Risk Indicators should be developed and finalized in a timely manner (i.e. during study planning), using cross-functional collaboration.

a. Determination of Thresholds for a Specific Risk Indicator

- An expected value (e.g. rate, number, or range) must be ascertained.
- Thresholds can be adjusted depending on the study.

b. Attention to Risk Indicators

- A dashboard should be able to provide the right level of information to the function/role performing a monitoring activity

c. Responses to Thresholds

- When a given Threshold is reached, a decision needs to be made
- The choice, depending on the issue, (continue Central or Off-site Monitoring ??) for potential trends.
- Determine a specific response or action to each Threshold.
- Once determined, the decision for risk mitigation should be made.

Risk Indicators	
Categories	Variables to be Assessed (with comparability across program / protocol / country / site, as outlined in the Integrated Quality and Risk Management Plan)
Safety	Suspected Unexpected Serious Adverse Reactions Non-serious Adverse Events Serious Adverse Events
Investigational Product	Concerns regarding accountability, dosing, administration, or compliance
Subject Recruitment and Discontinuation	Subject Recruitment Subject Discontinuation
Issue Management	Protocol Compliance General Issues
Data Quality	Abnormal Trends in Data CRF Completion Discrepancy Management
On-site Workload-Based Triggers	Workload-Based Triggers Per Monitoring Plan
Essential Documents	Concerns about processing or storage of essential documents
Staffing, Facilities, and Supplies	Concerns about staffing or supplies / equipment

Scenario 1

- Risk Indicator Category: Safety
- Per the IQRMP, the risk level for the Safety category is high
- Risk Indicator: Outlier / trend in number of Adverse Events (AEs) per subject or per site

Threshold	Examples of Action(s)
+/- 5% more/less than the average reported AE rate (Green)	No action
+/- 5.1 to 15% more/less than the average reported AE rate (Yellow)	No action Assess data remotely (e.g. determine if AE symptoms were listed as separate AEs versus entered as one diagnosis, consider if the site's subject population is associated with a higher than average number of AEs) Call the site Visit the site
Greater than 15% of the average reported AE rate (Red)	Assess data remotely Call the site Visit the site

Scenario 2

- Risk Indicator Category: Subject Recruitment and Discontinuation
- Per the IQRMP, the risk level for the Safety category is high
- Risk Indicator: Subject Discontinuation (outliers / trends in ratio of subjects discontinued to subjects randomized)

Threshold	Examples of Action(s)
5 to15% more/less than the expected ratio and at least 3 subjects discontinued (Green)	No action
15.1 to 30% more/less than the expected ratio and at least 3 subjects discontinued (Yellow)	No action Assess data remotely (e.g. check against the average discontinuation rate across sites) Call the site Visit the site
Greater than 30% more/less than the expected ratio and at least 4 subjects discontinued (Red)	Assess data remotely (e.g. review the reasons for discontinuation, determine if risk Thresholds were exceeded for other Risk Indicators) Call the site Visit the site

Scenario 3

- Risk Indicator Category: Data quality
- Per the IQRMP, the risk level for the Safety category is high
- Risk Indicator: Discrepancy Management – Query response time

Threshold	Examples of Action(s)
< 5 days (Green)	No action
5 to 30 days (Yellow)	No action Assess data remotely (e.g. check against Risk Indicator for 'Visit date to CRF completion date') Call the site Visit the site
Greater than 30 days (Red)	Assess data remotely (e.g. determine if other risk Thresholds were exceeded, compare against the rate for other sites) Call the site Visit the site

4. Risk-based Monitoring Plan

- Created by the clinical monitoring group
- Includes trial-specific instructions for Monitors including monitoring activities that are conducted to mitigate risks, aligned with Overall Risk Level during various stages of trials
- Include those activities conducted Centrally, Off-site, and On-site
- On-site Monitoring Activities are conducted based on
  - timing of study activities
  - workload, or targeted Risk Indicators
  - conducted on a predetermined timeframe
- Off-site and Central Monitoring is ongoing and such activities can be targeted or can occur at fixed intervals

Risk-based Monitoring Plan

On-site Monitoring Activities

- On-site monitoring focus on workload and safety concern, based on information from Off-site and central data review.
  - Source Documentation
    - Ranges to consider what source of data on site is verified
    - SDV or SDR based on either observation or triggers
    - Subject-level safety information (SAE)
  - Consent Forms
    - Size of sample based on risk/issue identified
  - Investigational Product (IP)
    - Verify protection of the blind
    - Correct subject assignments
    - IP's date and logs
  - Essential Documents On-site File

Risk-based Monitoring Tools

Criteria for choosing RBM Tools

1. Ensure it's baseline risk assessment process examines the risk indicators set out

2. Ensure it can support both on-site and centralized monitoring

3. Ensure it provides a process for systematic review of the trial's risk profile

4. Ensure it is cost efficient

Author	Affiliated clinical trial Organ:	Risk assessment tool	Publication/ Marketing Year	Country of Origin	Applicable clinical trial phase	Applicable to med: devices	Mode of administration	Language	Cost	Quality check process
Brosteanu et al.	Academic	Risk analysis form	2009	Germany	All	Yes	Paper based	Eng: & Ger:	None	Ongoing: Non-inferiority testing
TransCelerate BioPharma Inc.	Biopharmac-eutical-(NPO)	Risk Assessment Categorization Tool	2014	USA	All	Yes	Electronically via Microsoft Excel	Eng:	None	No
JMP	ISV	JMP® Clinical	2010	USA	All	Yes	SaaS	Eng: & Chin:	Hosting fees	In-house validation
Cynteg rity	ISV	Early bird	2014	Germany	All	Yes	SaaS: operates independent to EDC system	Eng:	free for risk assessment Questionn:	In house validation and as part of PUEKS

Risk Assessment Categorization Tool (RACT)

- To facilitate risk assessment and risk mitigation by
  - Determine the risks that could affect subject safety, data quality or regulatory compliance
  - Identify how and by which function(s) the risks will be managed
  - Document risk mitigations in the individual functional plans forming Integrated Quality Risk Management Plan (IQRMP) (e.g. Data Review Plan, Statistical Analytical Plan, Safety Plan)

Risk Categorization and Application to Monitoring Activities

Monitoring Activity	High Risk	Medium Risk	Low Risk
Validation and Review of Data (Central/Off-site)	100%	100%	100%
SDV of Critical Data for First Randomized Subject	>75-100%	>50-75%	0-50%
SDV of Critical Data for Subsequent Randomized Subjects	>15-25%	>5-15%	0-5%
SDR of Critical Data for First Randomized Subject	>75-100%	>25-75%	0-25%
SDR of Critical Data for Subsequent Randomized Subjects	>25-40%	>10-25%	0-10%
Informed Consent Review	>75-100%	>50-75%	20-5%

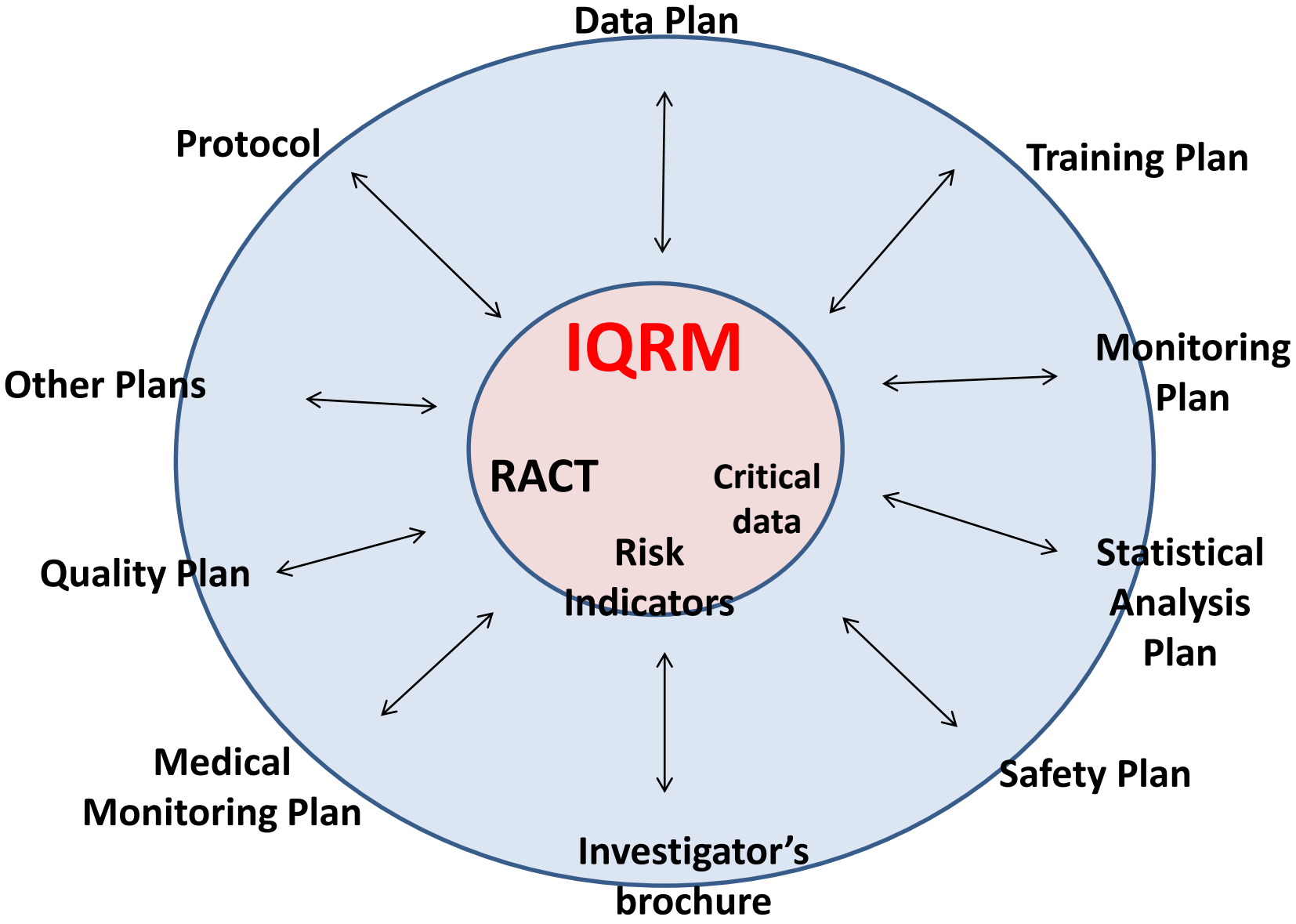
Integrated Quality Risk Management Plan (IQRMP)

- Tailored and integrated plan for a specific clinical trial:
  - Include the clinical and medical risks identified
  - Define the actions (proactively identify, assess, and manage risk throughout the clinical trial
  - Define the Critical Data identified by cross-functional representatives
  - Align associated quality management plans (including the Monitoring Plan) to ensure cross-functional teams focus on the risks (subject safety, data quality and regulatory compliance)
  - Describe the process that each function will follow to review and revise the IQRMP throughout the life of the clinical trial

- Inputs to the IQRMP:

  Clinical Development Plan
  Regulatory Strategy
  Risk Assessment and Categorization Tool
  Critical Data
  Any existing program or product risk management plans

IQRMP including RACT, Critical Data, Risk Indicators and Various Functional Plan



Recommended / Potential Risk Elements within the IQRMP

Key Elements of the IQRMP	Description	Location *(Provide link to document)*
Approval Section	Documents agreement and sign off by all relevant functions.	
Revision History	Provides version control and tracking.	
Critical Data	Defines and documents the Critical Data for the study. Critical Data is data that is critical to the reliability of the study findings, specifically those data that support primary and key secondary endpoints. Other Critical Data includes data critical to subject safety, such as serious adverse events and events leading to discontinuation of treatment.	
Medical Monitoring Plan	Describes clinical science/medical monitoring data review and cleaning activities.	
Safety Plan	Describes how pharmacovigilance/drug safety will manage safety risks related to a product.	
Data Plan	Describes the procedures for data collection/ review/cleaning.	

Recommended / Potential Risk Elements within the IQRMP

Key Elements of the IQRMP	Description	Location *(Provide link to document)*
Statistical Analysis Plan	Describes the procedures for executing the statistical analysis of the primary and secondary variables and other Critical Data.	
Monitoring Plan	Describes the remote/Off-site and On-site Monitoring Activities based on the identified risks. Includes Risk Indicators (triggers) that will help to drive decisions on the type of monitoring to be conducted.	
Training Plan	Describes the trial-specific training required of each party involved in the clinical trial, (e.g. Study Management teams, Monitors, Investigator Site Staff and Vendors).	
Quality Plan	Describe quality assurance/management activities. Provides tools and materials to ensure compliance to regulatory requirements and inspection readiness.	

Recommended / Potential Risk Elements within the IQRMP

Key Elements of the IQRMP	Description	Location *(Provide link to document)*
Other Functional Plans		
Risk Management Log	A tool used by the cross-functional team to track and monitor risk management, including the progress and actions relating to identified risks.	
Communication Plan	Describes the pathway for communicating and escalating issues.	

- IQRMP Revision and approval histories should be maintained.

Examples of different types key risks to be monitored & categorization

Site Performance Risks	Data Quality Risks	Patient Profile
Subject recruitment/ randomization	Missing Critical Data- Patient eligibility, critical efficiency, safety data points, eg. BP, HbA1c	Review of listing of AE/SAE for patients
Protocol deviation/violation per subject	Key efficacy end point data- data outliers /inconsistency	Review of listing of critical efficacy data points for patients
CRF completion/ incompletion rate- %CRF	Correlation check for critical variables	
Subject Discontinuation- site wise % discontinuation	AE/SAE under or over reporting	
Subject visits – outside window period	Data reporting	
Subject Screening Failure Rate	Data related to medical history & concomitant medications	
Open Queries Status	Missing data points-key demographics data	
Electronic data capture history		

Example for Overall Risk Level Scoring

Category (Weighting %)	Study A *Phase III, endpoint/ mortality study*	Study B *Phase IV, some remote data entry by subjects*	Study C *Phase II, well-known population, well-categorized disease state*
Safety (xx%)	high	low	high
Study Phase (xx%)	med	low	high
Complexity (xx%)	med	low	med
Technology (xx%)	low	med	low
Subject Population (xx%)	high	low	med
Data Collection (xx%)	low	low	low
Endpoints (xx%)	high	low	med
Overall Risk Level	**high**	**low**	**med**

Examples of risk reports and thresholds for Central Monitoring

Risk (KRI, CSM)	Type of Reports to be Monitored	Threshold
Subject recruitment/randomization rate (per month/per site)	Site wise bar graph– average recruitment rate per month (total patient recruited / total months of recruitment)	< 2 pts/month/site or > 5 pts/month/site or >20% sites below expected recruitment rate
CRF Completion/Incompletion - % CRF incomplete rate	Site with bar graph– % CRF pages completed and % of incomplete CRFs with aging period	> 10 days pending: =>20% CRFs
Adherence to key eligibility criteria	Table showing subject ids (not fulfilling key eligibility criteria)	=>1 patient not fulfilling eligibility criteria
Key efficacy data points reporting	Distribution graph showing outliers (site level)	=>1 site with outlier/s
AE/SAE under or over reporting	Site wise report representing per patient AE/SAE rate over duration	=>1 site with outlier/s
Subject Discontinuation	Site wise bar graph showing actual and % of discontinuation rate	>7% of subjects discontinued

Potential events leading to change in planned on-site monitoring

Risk/Issue Area	Examples Of Events/Incidences
Site performance	Site/s recruiting very higher number of patients (higher PRR than expected) Site/s with significantly high screening failure rate Site/s with high patient discontinuation rate
Data quality	Site/s showing continuous outlier, inconsistencies or abnormal distribution of critical efficacy & safety data Site/s missing critical data points (missing data)
Patient safety	Site/s showing higher or lower per patient AE/SAE rate than other sites Site/s missing SAE reporting in time Site/s with significant number of patients discontinued due to AE/SAEs
Study conduct /protocol specific study procedure deviation/violation	Site/s not performing protocol specific procedure on time (e.g. for a study , MRI to be taken exactly 1 hr after study drug intake)
Important protocol deviation or violation	Site/s recruiting patient not fulfilling key eligibility criteria Site/s showing patients' visits happening consistently out of window period
Patient compliance	Site/s with patients with missing study drug administration Site/s with patients missing subject diary

Major Pitfalls in Risk-Based Monitoring

1. Risk evaluation is subjective.

2. Bias is when an interested party is involved in the evaluation.

3. Risk evaluation becomes outdated. The risk landscape changes during a trial.

4. Late data arrival. Danger - patient safety.

5. Engaging and involving sites in the RBM initiative is critical to its success.

6. Monitoring team does not accept the new procedure.

How to Implement RBM

1. Find a champion and an executive sponsor
- Realize the need for change, understand its potential and then form the way for change

2. Get the right tools
- Best to start with tools that offer fast, visual results without the need for extensive database, programming or even statistical experience.

3. Start small
- Start with a single study or small group of studies

4. Scale up gradually
- This approach is much less threatening than a single, dramatic shift, and the ability to learn better processes.

Consideration for adaption of RBM

- Do you have the analytical expertise to monitor data centrally?
- Do you have the tools to build a useful dashboard?
- How do you gather and transmit the data from test sites?
- What happens to the people conducting on-site reviews today?

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